

The EU-ToxRisk project

A European flagship program for mechanism-based safety sciences and risk assessment

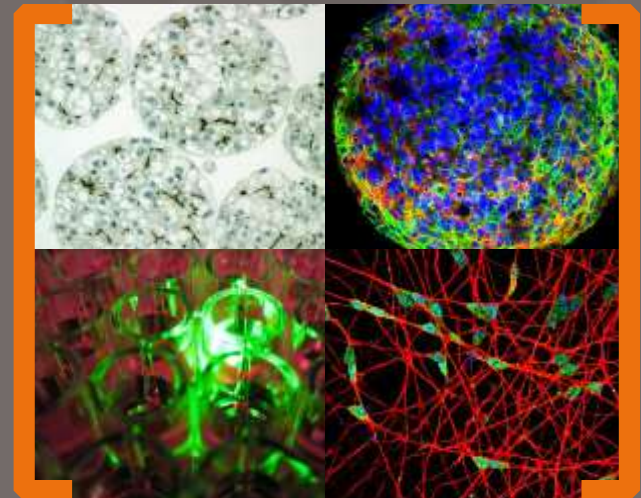
Case studies

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Horizon2020 Health call PHC-33:

New approaches to improve predictive human safety testing

Expected outcome

More **effective, faster, cheaper toxicological testing** to better **predict human risk** and meet regulatory needs.

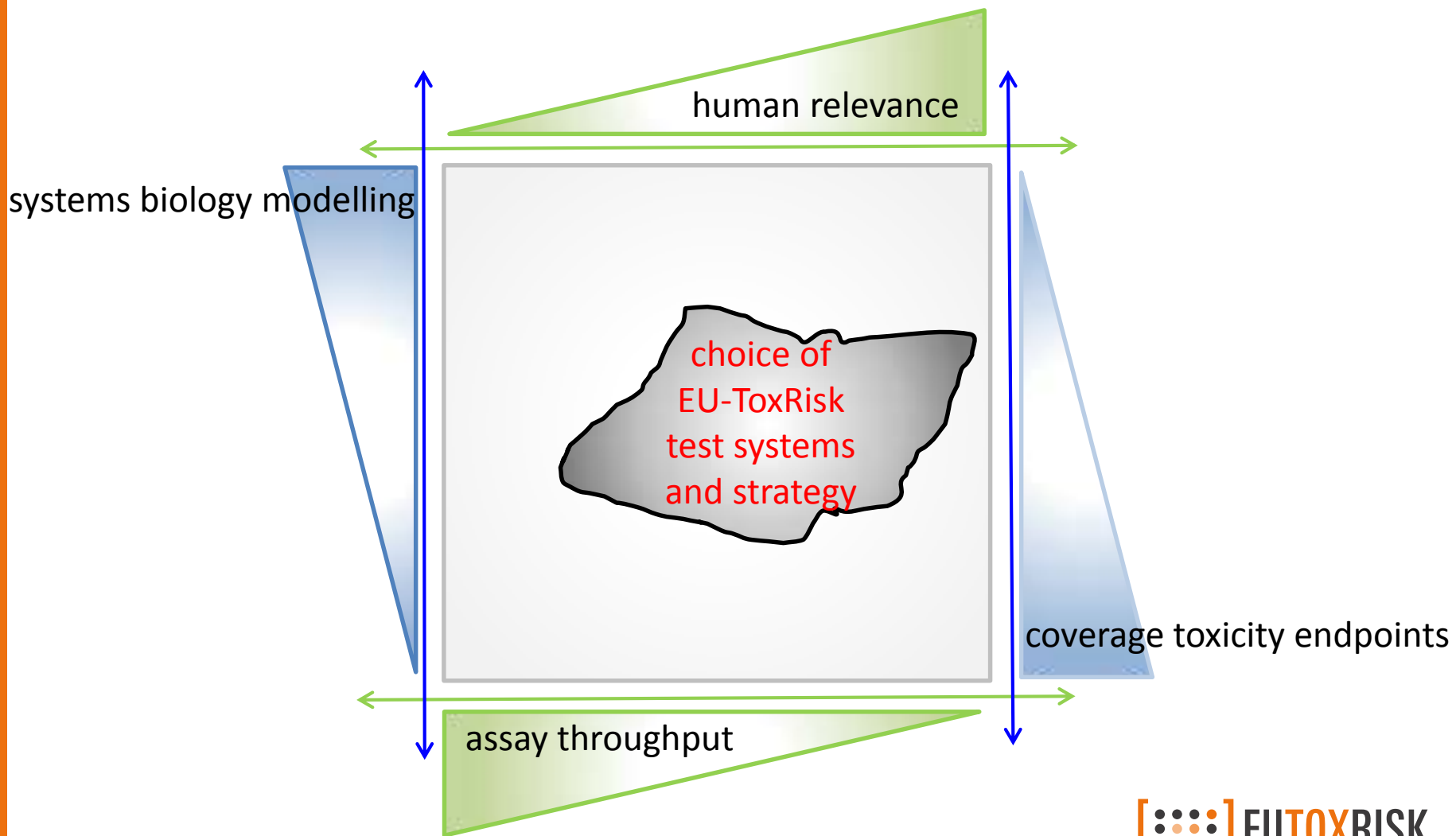
Improved **toxicological knowledge to encourage 'read across'** between chemical substances for use in different research and regulatory domains.

Commercial exploitation of the developed toxicological testing methods and assessment approaches, products and services.

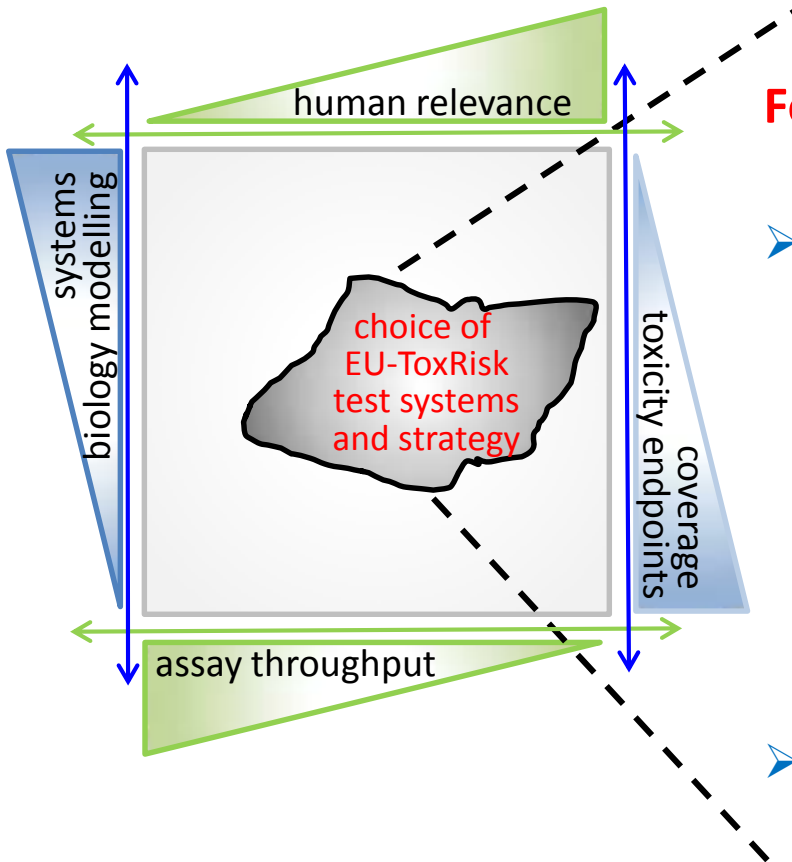
Advancement of **international co-operation** in the field of predictive toxicology and human safety testing.

Reduced use of laboratory animals in safety testing.

EU-ToxRisk strategic choices



EU-ToxRisk focus areas



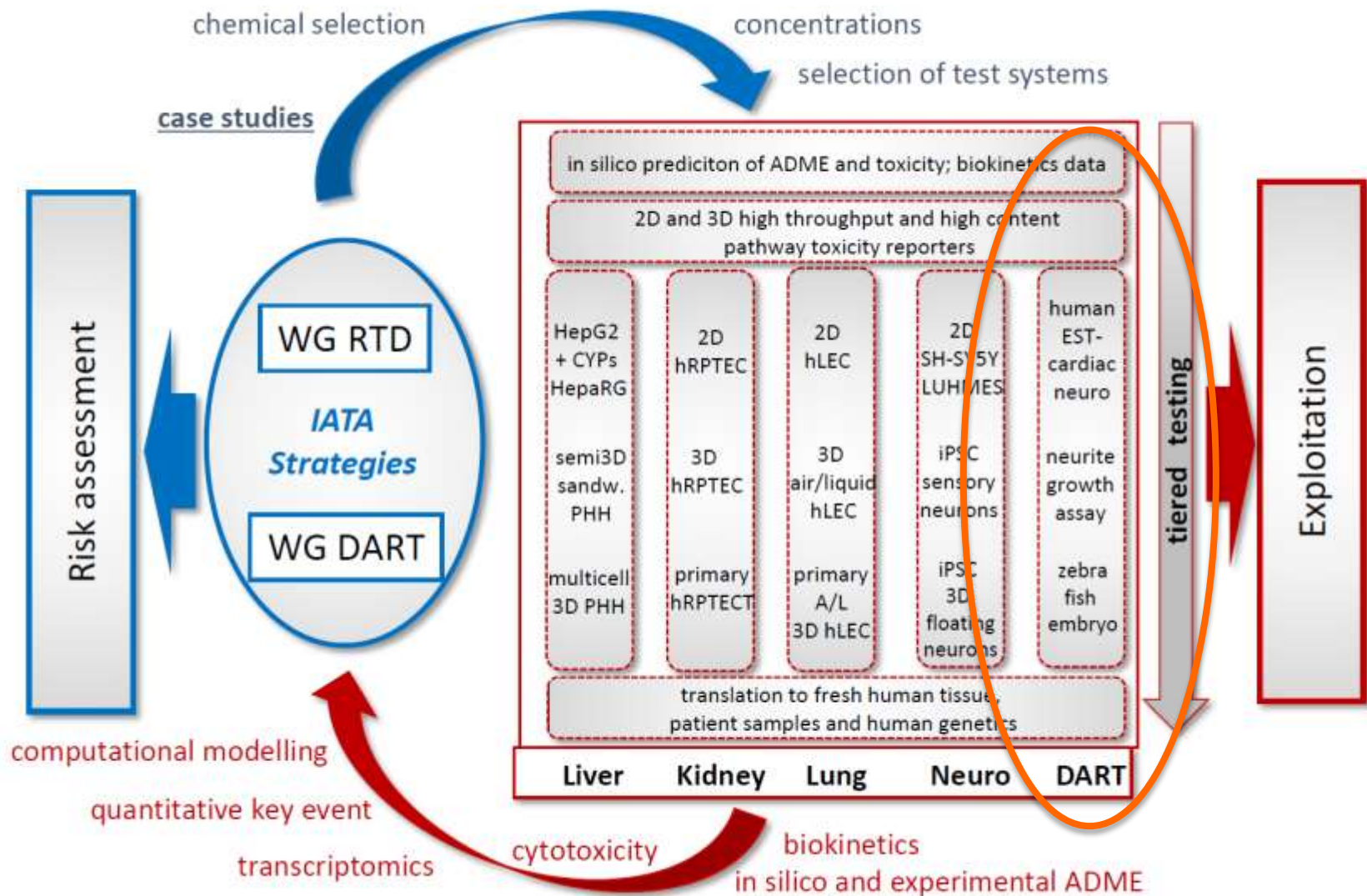
Focus areas for improved risk assessment:

➤ Repeat Dose Toxicity (RDT)

- Liver
- Kidney
- Lung
- Neuro

➤ Developmental and Reproductive Toxicity (DART)

EU-ToxRisk will proceed on a test battery approach



EU-ToxRisk DART test battery

human
EST-
cardiac
neuro

neurite
growth
assay

zebra
fish
embryo

EST = Embryonic Stem Cell Test
(general developmental assay – UKN1)

NeuriTox = human neuronal axon growth

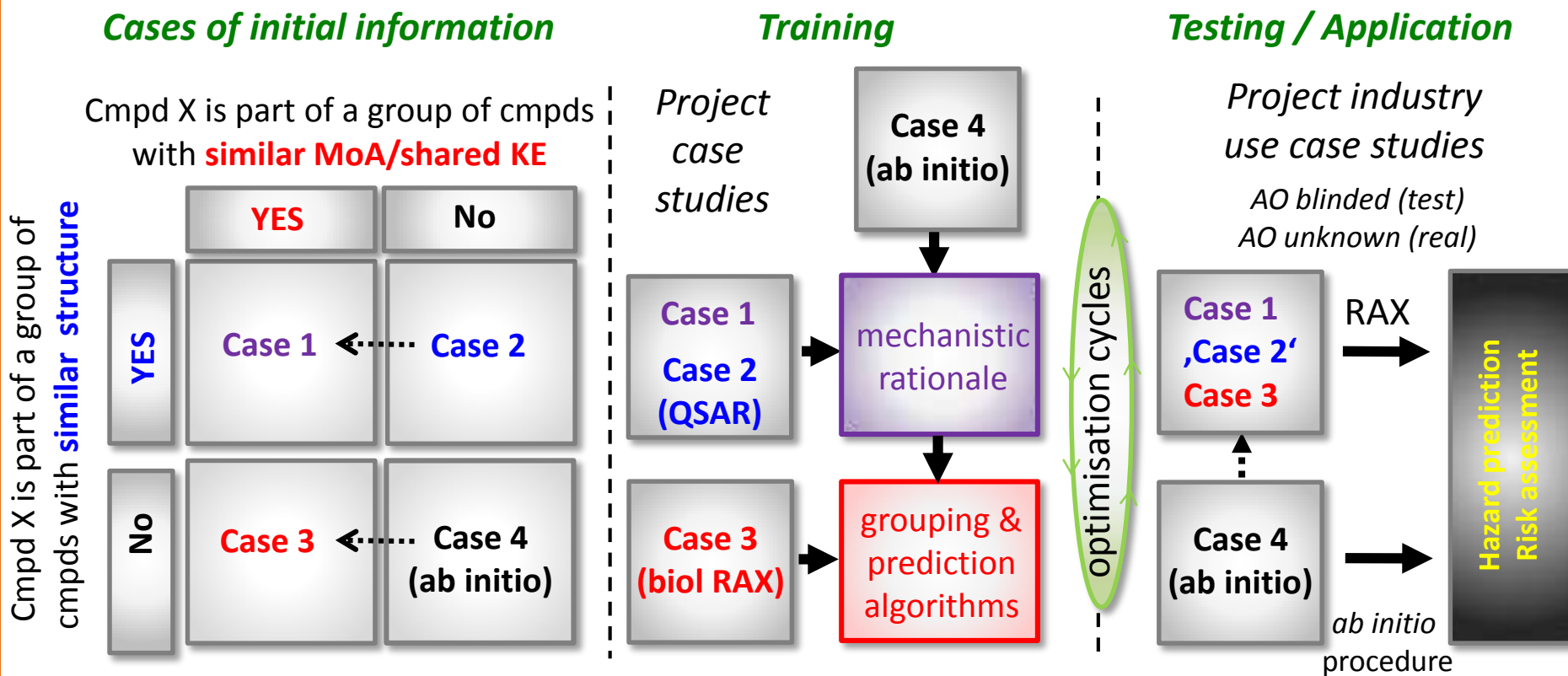
MINC = human neural crest function

ZFE = Zebra fish embryo
(OECD developmental toxicity assay)

ZFE = Zebra fish embryo – fluorescent reporters
(mechanistic / HTS assays)

Nuclear receptor activity
Developmental signaling screen

Case studies as drivers of EU-ToxRisk



Case studies for Scientific Concepts

Case studies to address the following **Scientific Concepts**:

1. Develop improved **read across strategies** to predict toxicity
2. Develop rapid and reliable prediction whether **metabolism** plays a major role in RDT / DART
3. Explore/explain (predictiveness) the **relation** between **acute effects** and RDT / DART
4. Predict human **blood concentrations (and doses)** that cause an increased risk of RDT (*liver, kidney, neuro, lung*) or of DART
5. Link known and unknown toxicants to existing and new **AOP**
6. **Link** triggering of AOP via **ADME** to human dose, and define predictivity of our instruments
7. Predict the correct **most critical adverse** effect in an inter-organ test set-up → to obtain the PoD for risk assessment

Case studies as drivers of IATA

These Case Studies will be used to develop **Workflows**

Workflows will be used to develop **IATA (ITS)**

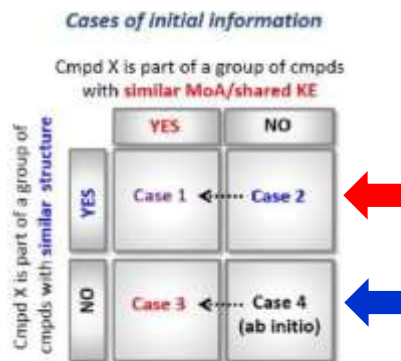
IATA: Integrated Approach to Testing and Assessment
(ITS: Integrated Testing Strategies)

IATA (ITS) are to characterize a chemical's toxicological profile based on an *in silico* and *in vitro* methods approach

Recommendations for all case studies:

- Clear description of case study purpose, esp. regulatory assessment
- Develop work plan (experimental work, milestones)
- Develop success-/ stop-criteria
- Suggest compounds as negatives for other case studies
- Involvement of regulators in case study discussion
- If possible, use common model systems; (some) compounds should be tested in all model systems
- Fit case studies to modeling needs (and *vice versa*)
- Take into account TG GATEs, OPENPHACTS data, etc..
- Consider mock submissions to regulatory authorities
- *etc ...*

First set of case studies



RDT

Liver: Steatosis / Valproic acid analogues

Liver & Kidney: Oxidative stress / Hydroquinones, resorcinols

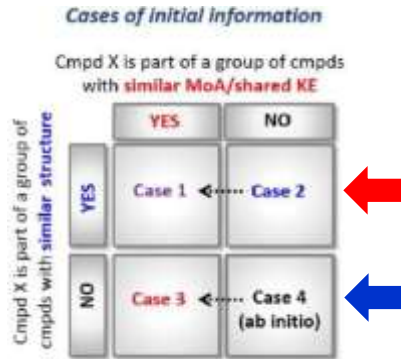
Unspecified toxicity / Alkylated phenols

Liver & Kidney: Peroxis.prolif. / Phenoxy carboxylic acids

Liver: Diverse mechanisms / various 'hepatotoxicants'

All organs: Mitochondrial toxicants

First set of case studies



DART

Fetus: a.o. Neural Tube Defects /

Valproic acid analogues

Fetus: Endocrine Disruptors / 'Conazoles'

Next set of proposed case studies

RDT

Lung: 'popcorn lung' / Diacetyl analogues

All organs: Microtubule disruption / diverse chemicals

Kidney: Proximal tubule cell toxicity / Amino glycosides

Neurons: Trans-axonal transport inhibition ? / Acrylamides

SEURAT-1 case studies

DART

Yet to be defined; identification via use of P&G framework

Cosmetics Europe case studies (parabens....)  EUTOXRISK

Exploratory studies

- “Case studies light”
- Easier to start, less stringent re interdisciplinarity and regulatory requirements
- Two types of exploratory studies:
 1. Studies based on initiated projects within partner labs (not currently part of another funded project)
 2. Studies started from scratch to clarify pivotal questions before a full case study is initiated (*PoC new assays; verify literature findings; test new computational model ...*)

Some proposed exploratory studies

1. Neurotoxicity 80 NTP compounds library: *potential regulatory use of screen data*
2. Organochlorine compound read across: *RAX non-planar PCBs*
3. Steatosis: *AOPs for non-VPA analogues*
4. Immune-related DILI: *can we predict this?*
5. ..

Conclusions

First case studies, focussing on read across, matured and running

New set of *candidate* case studies identified

New set of *candidate* exploratory studies identified

Case study selection strategy RDT and DART *in preparation*

Concept IATA RDT and DART *in preparation*

Thank you

